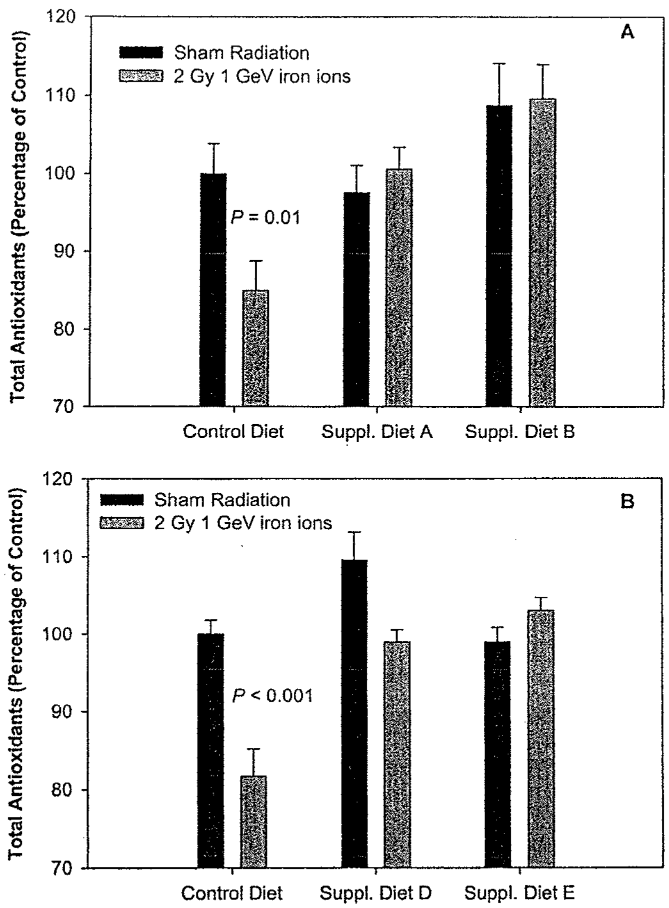

FIG. 6. Effects of diets A, B, D and E on the total antioxidant levels in Sprague-Dawley rats irradiated with 1 GeV/nucleon iron ions. The animals were fed diet C (control diet), diet A (supplemented with SeM at 12 μg per gram of diet in combination with selected antioxidants), or diet B (supplemented with SeM at 12 μg per gram of diet) for 3 days in one experiment with 1 GeV/nucleon iron ions (panel A) and fed with diet C, diet D (supplemented with SeM at 0.06 μg per gram of diet in combination with selected antioxidants), or diet E (supplemented with SeM at 12 μg per gram of diet) for 4 days in the other experiment with 1 GeV/nucleon iron ions (panel B). The animals were then irradiated with 2 Gy of 1 GeV/nucleon iron ions and killed 4 h after irradiation by carbon dioxide inhalation. Blood samples were collected by cardiac puncture, and serum (panel A) or plasma (panel B) was prepared for the measurement of total antioxidants using the Randox assay kit. Five rats were used in each treatment group at each dose, and the results are presented as means ± standard errors (SE). The average levels of total antioxidants in plasma were 0.61, 0.52, 0.60, 0.61, 0.66 and 0.67 m*M* HTCA equivalent for the six treatment groups shown from left to right in panel A, and 0.64, 0.53, 0.71, 0.64, 0.64 and 0.66 m*M* HTCA equivalent for the six treatment groups shown from left to right in panel B. The *P* value indicated was derived from a *t* test that compared each treatment group with the sham-irradiation (0 Gy) control group of rats fed the control diet.

These results are comparable to those observed in the γ-ray experiments in that SeM can partially prevent the radiation-induced reduction in total antioxidants and the combination of dietary supplements is somewhat more effective than SeM alone in preventing radiation-induced oxidative stress.

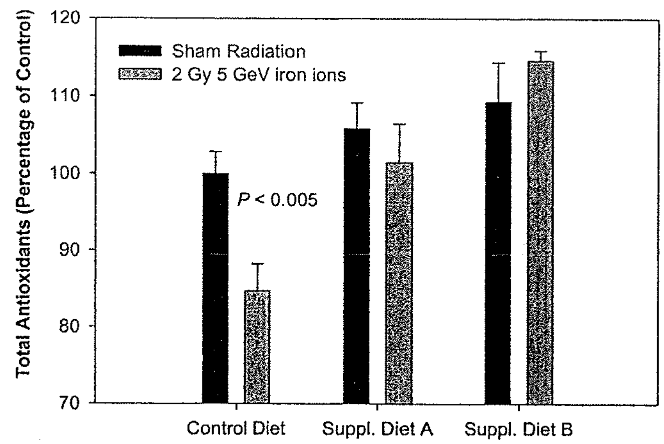

FIG. 7. Effects of diet A and diet B on the total antioxidant levels in Sprague-Dawley rats irradiated with 5 GeV/nucleon iron ions. The animals were fed diet C (control diet), diet A (supplemented with SeM at 12 μg per gram of diet in combination with selected antioxidants), or diet B (supplemented with SeM at 12 μg per gram of diet) for 3 days and then were irradiated with 2 Gy of 5 GeV/nucleon iron ions. Animals were killed 4 h after irradiation by carbon dioxide inhalation. Blood samples were collected by cardiac puncture and sera were prepared for the measurement of total antioxidant status using the Randox assay kit. Five rats were used in each treatment group at each dose, and the results are presented as means ± standard errors (SE). The average levels of total antioxidants in plasma were 0.51, 0.43, 0.54, 0.52, 0.56 and 0.59 m*M* HTCA equivalent for the six treatment groups shown from left to right. The *P* value indicated was derived from a *t* test that compared each treatment group with the sham-irradiation (0 Gy) control group of rats fed the control diet.

Exposure of the animals fed the control diet to radiation with 1 GeV/nucleon or 5 GeV/nucleon iron ions at a dose of 2 Gy decreased the total antioxidants in serum (Figs. 6A and 7) or plasma (Fig. 6B) by approximately 15 to 18%, and the decrease was statistically significant ($P = 0.01$ or less). For the animals fed diet A, B, D or E, no significant decrease was observed in the total antioxidants in plasma or serum after the HZE-particle exposure ($P > 0.05$). These results are consistent with those observed in the γ-ray and proton experiments except that SeM supplementation by itself at a level as low as 0.06 μg per gram of diet was as effective as the combination of supplements in preventing the HZE-particle-induced decrease in total antioxidants.

DISCUSSION

We have previously developed a sensitive dichlorofluorescein (DCF) fluorescence assay that can be used to detect radiation-induced oxidative stress *in vitro* at radiation doses as low as 1.4 cGy (*12*).[2] For *in vivo* studies, there are many biomarkers for detecting oxidative damage produced by radiation, such as lipid peroxidation (LPO) products, DNA-hydroxylation products (8-hydroxy-2′-deoxy-

[2] X. S. Wan, Z. Zhou, J. H. Ware and A. R. Kennedy, Standardization of a fluorometric assay for measuring oxidative stress in irradiated cells. Manuscript submitted for publication.

guanosine), and the level of oxidized proteins (e.g. the protein carbonyl content) (*13*). Since these biomarkers may be produced subsequent to a depletion of cell antioxidant defense systems due to the increased production of free radicals and ROS in the irradiated animals, the level of antioxidants in the circulation may be a more sensitive and earlier biomarker of oxidative damage compared to the measurement of oxidized products.

Several reports have indicated that radiotherapy or whole-body irradiation is associated with an excessive increase in oxidative stress and a decrease in the levels of plasma and tissue antioxidants (*14–16*). In the present study, the effect of ionizing radiation on the serum or plasma levels of total antioxidants was first evaluated in Sprague-Dawley rats using a γ-ray source, since this type of radiation is readily available for routine experiments. The results demonstrate a dose-dependent decrease in the total antioxidant levels in plasma at 4 h after irradiation. The total antioxidant levels in plasma showed little change during the first 3 h after radiation exposure, indicating a delay before the depletion of antioxidants becomes measurable after the radiation exposure. A decrease in the plasma or serum levels of total antioxidants was also observed in Sprague-Dawley rats exposed to proton or HZE-particle radiation. The dose–response curves indicate a noticeable although statistically insignificant decrease of total antioxidant level at 10 cGy of γ rays or 1 GeV/nucleon iron ions, and the decrease in total antioxidants became statistically significant when the dose of γ rays and HZE particles increased to 1 Gy and 40 cGy, respectively. The doses of radiation expected to be received by an astronaut during a 90-day flight in low-Earth orbit or a 3-year mission to Mars are estimated to be approximately 11 cSv and 1 Sv, respectively (*17*), which are equivalent to 5.5 and 50 cGy assuming a relative quality factor (Q) of 2. Thus these expected doses to astronauts are close to the radiation doses evaluated in this study.

The time course of the change in plasma or serum levels of total antioxidants observed in the present study are generally comparable to the time course of the change in ascorbic acid and vitamin E levels previously reported in mouse bone marrow after whole-body X irradiation (*15*). This time course is quite different from those of DNA damage and repair, which are observed within milliseconds (*18*). The observed time course of radiation-induced changes in total antioxidants in plasma and serum is more consistent with the timeline of radiation-induced lipid peroxidation, which occurs of the order of hours after the radiation exposure (*19, 20*). The magnitude of the change in total antioxidant levels observed in our study is slightly lower than the 36% decrease in total antioxidants in serum reported for human patients who have undergone total-body irradiation in preparation for bone marrow transplantation (*16*). The smaller magnitude of the change observed in our study could be the result of a species difference or a difference in the radiation dose regimen used in the studies since the human patients received much higher radiation doses (up to 18 Gy of total accumulated dose at 1.5 to 5 Gy per fraction) than the rats (a single dose of 2 Gy) used in our study. In mice exposed to a single dose of 3 Gy whole-body X rays, the levels of ascorbic acid and vitamin E in bone marrow were reported to be decreased by 99% and 76%, respectively, at 24 h after irradiation (*15*). However, the serum levels of ascorbic acid and vitamin E in the mice remained unchanged after irradiation (*15*), suggesting that the radiation-induced change in antioxidant levels is probably a compartmentalized phenomenon, with bone marrow being a tissue that is highly susceptible to radiation-induced depletion of antioxidants. Despite the relatively smaller changes in total antioxidants in plasma or serum observed in the irradiated animals and human patients, the in total antioxidants in plasma or serum can be a very useful indicator of radiation-induced oxidative stress *in vivo* for space radiobiological research since plasma or serum samples are much easier to obtain from astronauts and animals than bone marrow.

Diet supplementation with antioxidants has been shown to reduce oxidative stress induced by many different environmental agents (*21–23*), suggesting a possibility that antioxidant supplementation may prevent oxidative stress induced by space radiation. Since radiation-induced oxidative stress is an early event that precedes most downstream events leading to tissue damage and other adverse biological effects, such as cancer development, preventing radiation-induced oxidative stress is likely to be effective for preventing radiation-induced adverse biological effects. Treatment with vitamin C was shown to be effective in preventing mutagenesis caused by oxidative stress (*24*). We have demonstrated previously that treatment with SeM can completely prevent transformation of HTori-3 cells induced by 5 GeV/nucleon iron ions (*25*). In this study, we observed that dietary supplementation with SeM alone partially prevented the reduction of total antioxidants in animals exposed to γ rays or protons, while a combination of selected antioxidants completely prevented the decrease in total antioxidant levels in Sprague-Dawley rats exposed to all three types of radiation sources used in this study. In one of the experiments with 1 GeV/nucleon iron ions performed in this study, diet supplementation with SeM, sodium ascorbate, *N*-acetyl cysteine, α-lipoic acid reduced form, vitamin E succinate, and co-enzyme Q10 at levels equivalent to 40% of the upper limit of safe human daily intake was shown to be sufficient for a complete prevention of the radiation-induced decrease in total antioxidants in plasma. These results suggest that SeM and antioxidant supplements can be a feasible and effective countermeasure against space radiation-induced oxidative stress with minimal risk of toxicity.

It is worth noting that the dose–response relationship between the total antioxidant levels in plasma and radiation dose is linear for γ rays but follows an exponential decay model for HZE particles. The different shapes of the dose–

response curves suggest the possibility that the depletion of total antioxidants in plasma caused by these two types of radiation might occur through different mechanisms. Unlike γ rays, which are sparsely ionizing radiations with low linear energy transfer (LET), HZE particles represent densely ionizing radiations with high LET. Due to the high density of ionization along the path of HZE particles that travel though tissues and body fluids, HZE particles are likely to be more effective in causing damage to tissues and biomolecules, as seen in various reports showing that HZE-particle radiation has a higher relative biological effectiveness (RBE) than low-LET radiation (*26–28*). Consequently, repairing the damage caused by a given dose of HZE-particle radiation may consume more antioxidants than repairing the damage caused by the same dose of low-LET radiation, thereby causing a steeper decline in the total antioxidant pool of the animals exposed to HZE-particle radiation.

In addition to the difference in the shapes of the dose–response curves for the antioxidant depletion caused by the γ rays and HZE-particle radiation, a subtle yet noticeable difference was also observed in the relative effectiveness of SeM in preventing the plasma antioxidant depletion caused by the different types of radiation. In the Sprague-Dawley rats exposed to 1 GeV/nucleon or 5 GeV/nucleon iron ions, SeM alone worked as effectively as the antioxidant combination (including SeM) in preventing the radiation-induced reduction of total antioxidants in plasma. In contrast, SeM was less effective than the combination of antioxidants in preventing γ-ray- and proton-induced reduction of total antioxidants. The cause for the difference is not clear.

In conclusion, our studies indicate that the oxidative stress induced by γ rays occurred in a time- and dose-dependent manner, and that exposure of Sprague-Dawley rats to 2 Gy of protons, HZE particles or γ rays caused comparable levels of oxidative stress in Sprague-Dawley rats. SeM alone or in combination with other agents can partially or completely prevent the decrease in serum or plasma levels of total antioxidants in Sprague-Dawley rats after exposure to γ rays, protons or 1 GeV/nucleon and 5 GeV/nucleon iron ions. Our results suggest that SeM and the formula of selected dietary supplements may have beneficial effects in astronauts during space flight.

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Effects of Dietary Supplements on the Space Radiation-Induced Reduction in Total Antioxidant Status in CBA Mice

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Guan, J., Stewart, J., Ware, J. H., Zhou, Z., Donahue, J. J. and Kennedy, A. R. Effects of Dietary Supplements on the Space Radiation-Induced Reduction in Total Antioxidant Status in CBA Mice. *Radiat. Res.* 165, 373–378 (2006).

In the present study, the total antioxidant status was used as a biomarker to evaluate oxidative stress induced by proton, HZE-particle and γ radiation in CBA mice. The results demonstrated that the plasma level of TAS was significantly decreased ($P < 0.05$) in CBA mice after exposure to a 50-cGy dose of radiation from HZE particles or a 3-Gy dose of radiation from protons or γ rays. Diet supplementation with Bowman-Birk Inhibitor Concentrate (BBIC), L-selenomethionine (L-SeM), or a combination of *N*-acetyl cysteine, sodium ascorbate, co-enzyme Q10 (CoQ10), α-lipoic acid, L-SeM and vitamin E succinate could partially or completely prevent the reduction in the plasma level of TAS in CBA mice exposed to proton or HZE-particle radiation. The selected antioxidant combination with or without CoQ10 has a comparable protective effect on the γ-radiation-induced drop in TAS in CBA mice. These results indicate that BBIC, L-SeM and the selected antioxidant combinations may serve as countermeasures for space radiation-induced adverse biological effects.

INTRODUCTION

Exposure to space radiation is of great concern for the health of astronauts. Space radiations of particular concern are protons and the energetic, heavy charged particles known as HZE particles. These types of ionizing radiation, as well as other types of ionizing radiation that are encountered on Earth, are capable of generating free radicals and reactive oxygen species (ROS) in cells. It is known that ROS can be highly damaging to DNA, lipids and proteins in living organisms. Cells can defend themselves against ROS with efficient antioxidant enzymes, which include superoxide dismutases (SODs), glutathione (GSH) peroxidases (GPx), catalase (CAT) and a variety of thiols and free radical scavenging agents (*1–3*). There is a balance that exists between oxidants and antioxidants under normal physiological conditions in healthy people and other organisms. Exposure to space radiation, however, is capable of shifting this balance in favor of oxidants (*4*). We have previously reported that both protons and HZE particles are capable of inducing oxidative stress in cultured human breast epithelial cells (*5*) and decreasing the serum/plasma level of TAS in irradiated Sprague-Dawley rats (*6*). These findings indicate that antioxidant agents may be used to protect against space radiation-induced adverse biological effects.

The Bowman-Birk protease inhibitor (BBI) is an 8-kDa soybean-derived protease inhibitor with anticarcinogenic (*7–9*), anti-inflammatory (*10*) and radioprotective properties (*11–13*). BBI concentrate (BBIC) is a soybean extract containing high levels of BBI (*14*). We have previously observed that BBI and BBIC can inhibit superoxide anion radical generation in HL-60 cells; these agents do not, however, act as simple free radical scavengers (*15*). In the present study, we chose CBA mice as the animal model and the plasma TAS as the biomarker of oxidative stress to evaluate the effects of BBIC, L-SeM and the selected antioxidant combination on space radiation-induced oxidative stress *in vivo*. Due to the conflicting evidence about whether orally administered CoQ10 can significantly enhance its tissue levels *in vivo* (*16–18*), in the present study we also compared the protective effects of the antioxidant combination with or without CoQ10 against radiation-induced oxidative stress in CBA mice exposed to γ radiation.

MATERIALS AND METHODS

Chemicals and Total Antioxidant Assay Kits

L-SeM, sodium ascorbate, *N*-acetyl cysteine, α-lipoic acid, vitamin E succinate, and CoQ10 were purchased from Sigma Chemical Company (St. Louis, MO). Total antioxidant status assay kits were purchased from Randox Laboratories Ltd. (Oceanside, CA).

Animal Food Preparation

The AIN-93G rodent diet was used in these studies; this diet is commonly used for NCI-funded cancer chemoprevention studies in animals. The AIN-93G diet was purchased from Bio-Serv (Frenchtown, NJ). The control diet (referred to as diet C) and four supplemented diets (referred to as diets A, B, D and E) were prepared in-house by mixing 1,000 g of

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powdered AIN-93G rodent diet and 300 ml of water with or without the dietary supplements. The mixture was reshaped into pellets and then dried in air at room temperature for a minimum of 3 days before being used in the animal experiments. Diet A was AIN-93G rodent diet with additional supplementation of L-SeM (0.14 μg/g diet), sodium ascorbate (17.14 μg/g diet), *N*-acetyl cysteine (51.43 μg/g diet), α-lipoic acid (102.86 μg/g diet), vitamin E succinate (8.57 μg/g diet), and CoQ10 (51.43 μg/g diet). Diet B was AIN-93G rodent diet supplemented with L-SeM (0.14 μg/g diet). Diet C was AIN-93G rodent diet without additional supplementation. The baseline level of selenium in AIN-93G rodent diet is 0.18 ppm (0.18 μg/g of diet) in the form of sodium selenate. Diet D was AIN-93G rodent diet with additional supplementation of BBIC (10 mg/g diet). Diet E was AIN-93G rodent diet supplemented with the same antioxidants as diet A but without CoQ10.

Animal Care and Treatment

Male CBA mice were purchased from Taconic Farms Inc. (New York) at 8 weeks of age. The animals were housed in the animal facilities at the University of Pennsylvania (for the γ-ray experiment) or the Brookhaven National Laboratory (BNL) (for the proton and 1 GeV/nucleon iron-ion experiments) and provided with standard care and free access to water and food (Laboratory Rodent Diet, 5001, Animal Specialties and Provisions, Quakertown, PA) for a minimum of 1 week for the animals to adapt to the new environment. After this initial adaptation period, the animals were randomly divided into treatment groups. The animals were then subjected to different food/radiation treatments according to the designs of the three animal experiments performed in this study. The animal care and treatment procedures were reviewed and approved by the Institutional Animal Care and Use Committees at BNL and the University of Pennsylvania prior to the performance of the experiments.

The first two animal experiments were carried out to evaluate the protective effects of the dietary supplement agents on oxidative stress induced by radiation from protons or 1 GeV/nucleon iron ions. For the proton radiation experiment, 48 CBA mice were divided into eight treatment groups with six animals per group. The animals were fed with diet A, B, C or D (with two groups on each diet) for 3 days, then irradiated with a proton source at a single whole-body dose of 0 (sham radiation control, with one group on each diet treatment) or 3 Gy (one group on each diet treatment). The animals were killed humanely 4 h after the radiation exposure by carbon dioxide inhalation. The blood was centrifuged to separate the plasma from blood cells, and the plasma samples were frozen at −70°C before being analyzed to determine the TAS. For the 1 GeV/nucleon iron-ion radiation experiment, mice were divided into eight groups with six animals each, placed on diet A, B, C or D for 3 days, and then irradiated with 1 GeV/nucleon iron ions at a dose of 0 (sham radiation control) or 50 cGy. Blood was collected by cardiac puncture, and plasma was prepared and stored as described above.

The third experiment was designed to determine whether the selected antioxidant combination with or without CoQ10 had a comparable protective effect on radiation-induced oxidative stress *in vivo*. The experiment was performed at the University of Pennsylvania using a ^{137}Cs γ-ray source with a dose rate of 1.41 Gy per minute. CBA mice were divided into six groups with six animals each, placed on diet A, C or E for 4 days, and then irradiated with γ rays at a dose of 0 (sham radiation control) or 3 Gy. Blood was collected by cardiac puncture, and plasma was prepared and stored as described above.

The proton radiation experiment was carried out using high-energy (1000 MeV) protons generated from the facility at BNL with a dose rate of 20 cGy per minute. The HZE-particle radiation experiments were conducted using 1 GeV/nucleon iron ion beams from the Alternating Gradient Synchrotron (AGS) at BNL with a dose rate of 40 cGy–2 Gy per minute. The animals that were used as the sham radiation controls were placed in the target areas of the radiation exposure facility for the same amount of time as used for the exposed animals, but the radiation source was not activated.

Assay of Total Antioxidant Status

The plasma TAS was determined by a colorimetric assay system that was developed by Randox Laboratories. This assay system is currently being used for analyses of bioreduction capacity in blood samples from astronauts (*19*). This assay is based on the principle that 2, 2′-azino-di-[3-ethylbenzthiazoline sulfonate] (ABTS®), when incubated with a peroxidase (metmyoglobin) and H_2O_2, produces ABTS®*+ radicals; these radicals have a relatively stable blue-green color which can be measured at 600 nm. In the presence of antioxidants, the formation of colored ABTS®*+ radicals is suppressed; the magnitude of the suppression is proportional to the antioxidant concentration in the reaction solution. The assay method described in the manufacturer's instructions was modified into a 96-well plate format with wells on each row assigned to reagent blank, standard or test samples to accommodate the need for simultaneous measurement of multiple samples. 6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (HTCA) was used in the assay as the standard, and the TAS levels measured in the samples were expressed as HTCA equivalent. To perform the assay, 4 μl of double-distilled water, standard solution, or serum/plasma sample was mixed with 200 μl chromogen solution (6.1 μ*M* metmyoglobin and 610 μ*M* ABTS®) in each well, and the plate was placed in a PowerWave340 Microplate Spectrophotometer (Bio-Tek Instruments, Inc.) for a minimum of 15 min, with the temperature maintained at 37°C to allow the temperature to reach equilibrium. To initiate the reaction, 40 μl of diluted substrate (100 μ*M* H_2O_2 in stabilized form) was applied into each well; the plates were shaken for 3 s and then read at a wavelength of 600 nm four times at 1-min intervals. The total antioxidant status in the samples, based on the slopes of the linear kinetic lines determined in the wells, was calculated as follows:

$$\text{Total antioxidant status (m}M\text{)} = \frac{\text{slope for blank} - \text{slope for sample}}{\text{slope for blank} - \text{slope for standard}} \times \text{concentration of standard.}$$

Data and Statistical Analysis

The data are presented as the mmol/liter 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid equivalent. The data are shown as means ± SE. The means of the sham radiation and radiation treatment groups for each diet were compared by an unpaired *t* test on a Microsoft Excel (2002 version) spreadsheet.

RESULTS

Effect of Dietary Supplement Agents on Proton or HZE-Particle Radiation-Induced Oxidative Stress in CBA Mice

In the proton radiation experiment, the plasma level of TAS in the mice fed the control diet was decreased by approximately 25% after the proton radiation exposure at a dose of 3 Gy (Fig. 1, $P < 0.05$). The plasma TAS of the irradiated mice fed diet A, B or D was not significantly different from that of the sham-radiation mice fed the same diet ($P > 0.05$). These results suggest that dietary supplementation with BBIC, L-SeM or the selected antioxidant combination can prevent the reduction in the plasma level of TAS associated with exposure to proton radiation.

Exposure of the animals fed the control diet to radiation with 1 GeV/nucleon iron ions at a dose of 50 cGy decreased the TAS in plasma (Fig. 2) by approximately 21%, and the decrease was statistically significant ($P < 0.05$). For the animals fed diet A, B or D, no significant decrease was

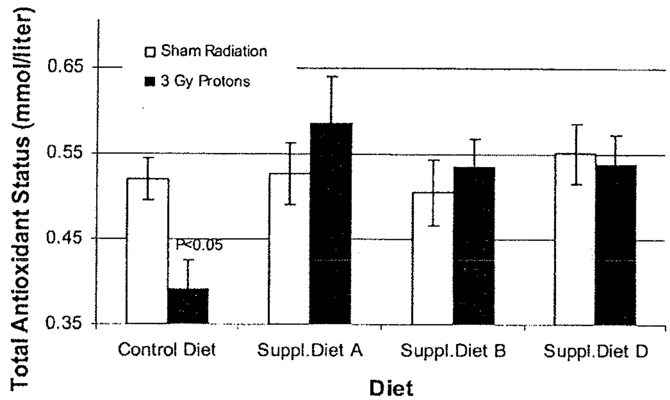

FIG. 1. Effects of diets A, B, C and D on the total antioxidant status in CBA mice irradiated with protons. The animals were fed diet A (supplemented with SeM at 0.14 μg per gram of diet in combination with selected antioxidants), diet B (supplemented with SeM at 0.14 μg per gram of diet), diet C (control diet), or diet D (supplemented with BBIC at 10 mg per gram of diet) for 3 days and were then irradiated with 3 Gy of protons. Blood samples were collected by cardiac puncture, and plasma was prepared for the measurement of total antioxidant status using the Randox total antioxidant status assay kit. Six mice were used in each treatment group, and the results are presented as means ± standard errors (SE). The *P* value indicated was derived from a *t* test in which the results from the irradiated group (3 Gy) were compared to the results from the sham-irradiated (0 cGy) group of mice fed each diet.

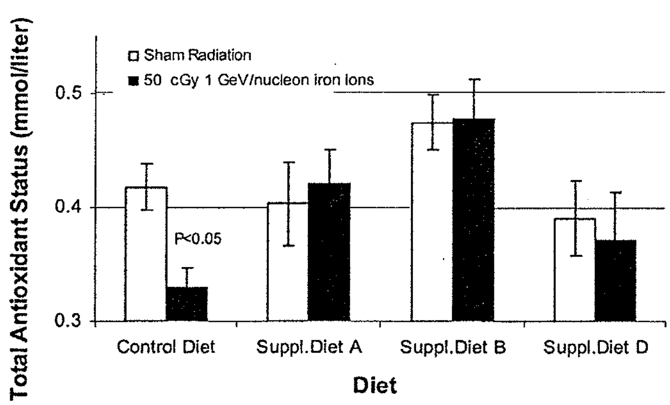

FIG. 2. Effects of diets A, B, C and D on the total antioxidant status in CBA mice irradiated with 1 GeV/nucleon iron ions. The animals were fed diet A (supplemented with SeM at 0.14 μg per gram of diet in combination with selected antioxidants), diet B (supplemented with SeM at 0.14 μg per gram of diet), diet C (control diet), or diet D (supplemented with BBIC at 10 mg per gram of diet) for 3 days and were then irradiated with 50 cGy of 1 GeV/nucleon iron ions. Blood samples were collected by cardiac puncture, and plasma was prepared for the measurement of total antioxidant status using the Randox total antioxidant status assay kit. Six mice were used in each treatment group, and the results are presented as means ± standard errors (SE). The *P* value indicated was derived from a *t* test in which the results from the irradiated group (50 cGy) were compared to the results from the sham-irradiated (0 cGy) group of mice fed each diet.

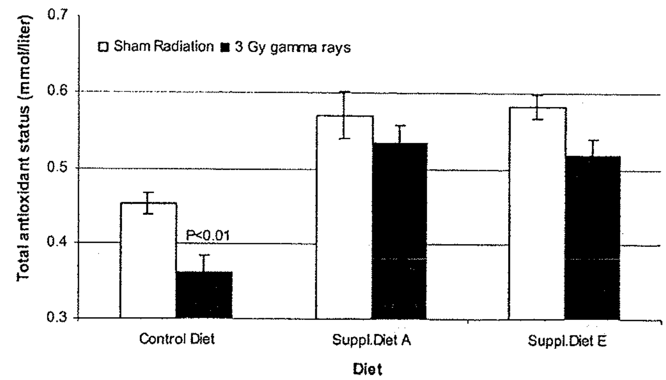

FIG. 3. Effects of diets A, C and E on the total antioxidant status in CBA mice irradiated with γ rays. The animals were fed diet A (supplemented with a selected antioxidant combination with CoQ10 at 51.43 μg/g diet), diet C (control diet), or diet E (supplemented with a selected antioxidant combination without CoQ10) for 4 days and were then irradiated with 3 Gy of γ rays. Blood samples were collected by cardiac puncture, and the plasma was prepared for the measurement of total antioxidant status using the Randox total antioxidant status assay kit. Six mice were used in each treatment group, and the results are presented as means ± standard errors (SE). The *P* value indicated was derived from a *t* test in which the results from the irradiated group (3 Gy) were compared to the results from the sham-irradiated (0 cGy) group of mice fed each diet.

observed in the plasma TAS after the HZE-particle radiation exposure ($P > 0.05$). These results are consistent with those observed in the proton radiation experiments.

Effect of the Antioxidant Combination with or without CoQ10 on γ-Radiation-Induced Oxidative Stress in CBA Mice

Exposure of the animals fed the control diet to γ rays at a dose of 3 Gy decreased the TAS in plasma (Fig. 3) by approximately 21% ($P < 0.01$). Supplementation with diet A or E prevented the drop in the plasma level of TAS in CBA mice exposed to γ radiation. The plasma level of TAS in mice fed diet A was comparable with that in mice fed diet E with or without radiation exposure ($P > 0.05$). These results suggest that a new formulation of antioxidant agents without CoQ10 may be as effective as the original formula with CoQ10 in preventing space radiation-induced oxidative stress.

DISCUSSION

We previously developed a sensitive dichlorofluorescein (DCF) fluorescence assay that can be used to detect radiation-induced oxidative stress *in vitro* at a radiation dose as low as 1.4 cGy (*20*). Based on this system, we have formulated an antioxidant combination containing *N*-acetyl cysteine, sodium ascorbate, CoQ10, α-lipoic acid, L-SeM and vitamin E succinate that is highly effective in protect-

ing against space radiation-induced oxidative stress *in vitro*[2] and in Sprague-Dawley rats (*6*). In the present study, the effect of the same supplement combination on space radiation-induced oxidative stress was evaluated in CBA mice as the animal model system. The doses used in this study were comparable to those expected from an extended space exploratory mission, with doses greater than 1 Sv over 3 years. The dose equivalent of radiation that is expected to be received by an astronaut during a 3-year mission to Mars is estimated to be approximately 1 Sv (*21*), which is equivalent to a dose of 50 cGy, assuming a relative quality factor of 2. The results presented in this report have shown that a dose of 50 cGy from HZE-particle radiation causes a comparable reduction in the plasma level of TAS in CBA mice to that observed for a dose of 3 Gy from protons or γ rays, which is consistent with the results from other studies showing that HZE-particle radiation has a higher relative biological effectiveness (RBE) than low-LET radiation (*22–24*).

It should be pointed out that the assay used in this study for TAS measurement is based on the principle that ABTS, when incubated with peroxidase and H_2O_2, produces $ABTS^{*+}$ radicals that can be measured at 600 nm. Theoretically, suppression of the $ABTS^{*+}$ radicals can be caused either by antioxidants that remove H_2O_2 from the assay system or by secreted factors capable of inhibiting the peroxidase activity in the assay system. If radiation exposure induced peroxidase inhibitor(s), the plasma samples from animals irradiated without antioxidant supplementation would have caused more suppression of $ABTS^{®*+}$ radical production than the plasma samples from sham-irradiated animals. Since such a phenomenon has not been observed in any of our radiation experiments, the suppression of the $ABTS^{*+}$ radical production measured in this study was interpreted as the indication of increased TAS.

Protons and γ rays are sparsely ionizing radiations with low linear energy transfer (LET), while HZE particles produce densely ionizing radiation with high LET. Due to the high density of ionizations along the path of HZE particles as they travel through tissues and body fluids, HZE particles are thought to be considerably more effective at causing damage to tissues and biomolecules than protons and γ rays. Consequently, repairing the damage produced by a given dose of HZE-particle radiation is likely to consume more antioxidants than those required for the repair of damage produced by the same dose of low-LET radiation, which would result in a greater decline in the total antioxidant pool of the animals exposed to HZE-particle radiation.

The bioreduction capacity constitutes the first line of cellular defense, which scavenges radiation-generated free radicals and reactive oxygen species or converts them into non-toxic molecules. When the bioreduction capacity is overwhelmed, free radicals and reactive oxygen species will accumulate to cause oxidative stress and damage cellular macromolecules (DNA, lipids and proteins) (*25, 26*). Several reports have indicated that radiotherapy or whole-body radiation is associated with an excessive increase in oxidative stress and a decrease in the levels of plasma and tissue antioxidants (*27–29*). There is some evidence that astronauts do deplete their vitamins during space flight, because there is a decrease in the plasma TAS in astronauts after long-duration space flights (*30*). In the present study, we observed that dietary supplementation with L-SeM or the formulated antioxidant combination could prevent HZE-particle- or proton radiation-induced oxidative stress in CBA mice, which is in agreement with the results from our previous animal studies using Sprague-Dawley rats (*6*). It is worth noting that the supplement combination with or without CoQ10 has a comparable protective effect on TAS reduction in γ-irradiated CBA mice, while our *in vitro* assay system indicated that CoQ10 was moderately effective at inhibiting radiation-induced oxidative stress in cultured breast epithelial cells.[2] The ability of antioxidants to act as effective protectors against oxidative stress *in vivo* is contingent upon their absorption and distribution in tissues and cells. Whether short-term oral administration of CoQ10 can enhance tissue amounts of CoQ10 remains controversial (*16–18*). Data from the present study support the idea that the antioxidant combination without CoQ10 was as effective as the antioxidant combination with CoQ10 at preventing the reduction in TAS in irradiated CBA mice. Since CoQ10 is very expensive, a new formula without CoQ10 will be less expensive for use during space travel. The results presented here suggest that the new formula without CoQ10 will be as effective as the original formula of antioxidants as a countermeasure against space radiation-induced oxidative stress.

In the present study, we also evaluated the effects of BBIC on TAS in CBA mice after exposure to proton or HZE-particle radiation. The results indicated that BBIC can prevent the radiation-induced reduction in the plasma level of TAS in CBA mice, which is consistent with the report that protease inhibitors can suppress oxidative damage (*31*). Several possible mechanisms can explain the protective effect of BBI on radiation-induced oxidative stress: (1) BBI might inhibit the production of free radicals in cells. Previous studies have shown that BBI can inhibit superoxide anion radical production in human polymorphonuclear leukocytes (PMN) (*32*) and differentiated HL60 cells (*15*). (2) BBI could be enhancing or inducing other radical-scavenging mechanisms. (3) BBI could be acting directly as a radical scavenger; this is conceivable as BBI has a very high cysteine content (14 of the 71 amino acid residues of BBI are known to be cysteine). However, our *in vitro* assays have suggested that BBI does not act as a simple free radical scavenger (*15*). The exact mechanism by which BBI

[2] X. S. Wan, J. H. Ware, Z. Zhou, J. J. Donahue, J. Guan and A. R. Kennedy, Protection against radiation induced oxidative stress in cultured human epithelial cells by treatment with antioxidant agents. Manuscript submitted for publication.

inhibits radiation-induced oxidative stress needs to be investigated further.

In conclusion, the results of the present study indicate that exposure of CBA mice to 50 cGy of HZE-particle radiation or 3 Gy of proton or γ radiation causes a comparable reduction in the plasma level of TAS in CBA mice. BBIC, L-SeM and the selected antioxidant combination with or without CoQ10 can partially or completely prevent the decrease in the plasma level of TAS in CBA mice after exposure to radiation from protons, 1 GeV/nucleon iron ions, or γ rays. Our results indicate that BBIC, L-SeM and the formula of selected dietary supplement agents protect against radiation-induced oxidative stress *in vivo*. Since radiation-induced oxidative stress is an early event that precedes most downstream events that can lead to tissue damage and adverse biological effects (e.g. cancer development), the prevention of radiation-induced oxidative stress by these agents may give some protection against the development of radiation-induced adverse biological effects in astronauts.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MONTANA
BILLINGS DIVISION

RON J. DUMONTIER, JOHN FUGLE, ANDREW HARVIE, DAVID HARVIE, DARREN HUGHSON, JOHN HARPER, TORY KJELSTRUP, TODD LOBREAU, ELBERT LOOMIS, ALLAN LUNGAL, WILLIAM L. ROBBINS, WILLIAM J. SCOFIELD, RON L. SMATHERS,

Plaintiffs,

vs.

SCHLUMBERGER TECHNOLOGY CORP.,

Defendant.

CV 04-16-BLG-RFC

ORDER

INTRODUCTION

This matter comes before the Court on Defendant's Motion to Dismiss Plaintiffs' Strict Liability Cause of Action and Substitute Sole Statutory Public Liability Cause of Action and Motion for Summary Judgment on Plaintiffs' Public Liability Cause of Action. Defendant first contends that with respect to an alleged radiological exposure, Plaintiffs are limited by federal statute to a Price-Anderson Act (Act) Public Liability Action (PLA) Claim. Defendant then

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EXHIBIT
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asserts that Plaintiffs' emotional distress and medical monitoring claims in conjunction with the PLA are barred because they require a present "bodily injury" which is absent in the present facts.

Plaintiffs counter that a PLA claim is not their sole remedy because the exposure in question may not be a "nuclear incident" under the statute, in which event the Act's preemption does not apply and the state law claim survives. Plaintiffs also argue that they sustained a physical injury or impact from their exposure to the ionizing radiation and even a minimal amount of radioactivity in the body represents a "bodily injury" at the sub-cellular level and is sufficient to survive summary judgment under a PLA.

FACTUAL BACKGROUND

Defendant Schlumberger Technology Corp. conducts well logging activities on drilling rigs in the vicinity of Havre, Montana. In the course of its well logging business, Defendant used a radioactive substance known as Cesium-137. Cesium-137 is normally shielded in a transportation container. On or about May 21, 2002, the Cesium-137 was left outside of its shielded container and remained on a drilling rig for an extended period of time while the rig was transported. Consequently, Plaintiffs allege they were exposed to unshielded radiation resulting in injuries and damages. However, aside from sub-cellular damage, no medical doctor is able to diagnose any known objective present medical condition caused by the radiation exposure.

I. DEFENDANT'S MOTION TO DISMISS PLAINTIFFS' STRICT LIABILITY CAUSE OF ACTION AND SUBSTITUTE SOLE STATUTORY PUBLIC LIABILITY CAUSE OF ACTION.

The Court must first determine if Plaintiffs are limited to the PLA claim as their sole cause of action. Defendant contends that because Plaintiffs' Amended Complaint asserts a

public liability as defined by 42 U.S.C. § 2014(hh), the PLA is the sole cause of action available to Plaintiffs and the state based strict liability cause of action should be dismissed.

Plaintiffs counter that the alleged exposure in this case might not qualify as a "nuclear incident" as defined in the statute and therefore the PLA's exclusivity does not control. In their Response to Defendant's Motion to Dismiss the Strict Liability Cause of Action, Plaintiffs concede that if the physical injuries and impacts alleged by Plaintiffs qualify as "bodily injuries" under the Act, then the incident was a "nuclear incident" and the PLA applies (*See Pltfs' Resp. p 5*). In their Response to Defendant's Motion for Summary Judgment Plaintiffs take the position that even low levels of radiation are capable of causing damage to DNA. (*See Plfts' Resp. p. 4*). Plaintiffs argue that a radiation dose above the Nuclear Regulatory Commission's dose limits for members of the public is a physical injury. *Id. at 3.*

The Act provides that, "[a] public liability action shall be deemed to be an action arising under section 2210 of this title, and the substantive rules for decision in such action shall be derived from the law of the State in which the nuclear incident involved occurs, unless such law is inconsistent with the provisions of such section." 42 U.S.C. § 2014(hh). The Act broadly defines a "public liability" and a "nuclear incident" as follows:

> [T]he term 'public liability' means any legal liability arising out of or resulting from a nuclear incident or precautionary evacuation ...." A nuclear incident is defined as, "**any occurrence**, including an extraordinary nuclear occurrence, within the United States **causing**, within or outside the United States, **bodily injury, sickness, disease, or death,** or loss of or damage to property, or loss of use of property, arising out of or resulting from the radioactive, toxic, explosive, or other hazardous properties of source, special nuclear, or byproduct material: ... ." 42 U.S.C. § 2014 (q) (Emphasis supplied).

The Act contains an unusual preemption provision that not only gives federal courts jurisdiction over tort actions arising out of nuclear accidents but also expressly provides for removal of such actions brought in state court even when they assert only state-law claims. *See* 42 U.S.C. § 2014(hh), *See also* El Paso Natural Gas Co. v. Neztsosie, 526 U.S. 473, 484-485, 119 S.Ct. 1430, 143 L.Ed.2d 635 (1999).

The Supreme Court has concluded that "the safety of nuclear technology [is] the exclusive business of the Federal Government...." Pacific Gas & Electric Co. v. State Energy Resources Conservation & Development Commission, 461 U.S. 190, 208, 103 S.Ct. 1713, 1724, 75 L.Ed.2d 752 (1983). The Seventh Circuit Court of Appeals has observed that, "state regulation of nuclear safety, through either legislation or negligence actions, is preempted by federal law." O'Conner v. Commonwealth Edison Co., 13 F.3d 1090, 1105 (7th Cir.), cert. denied, 512 U.S. 1222, 114 S.Ct. 2711 (1994). The Tenth Circuit Court of Appeals points out that, "the jurisdictional provisions of the PAA [the Act], 42 U.S.C. §§ 2014(w), 2210(n), as amended by the 1988 Amendments, appear broad enough to create a federal forum for any tort claim even remotely involving atomic energy production." Kerr-McGee Corp. v. Farley, 115 F.3d 1498, 1504 (10th Cir. 1997). Finally, the Ninth Circuit has held, "After the Amendments Act, no state cause of action based upon public liability exists. A claim growing out of any nuclear incident is compensable under the terms of the Amendments Act or it is not compensable at all." In re TMI Litig. Cases Consol. II, 940 F.2d 832, 854 (9th Cir.1991). By passing the Act, Congress created an exclusive federal cause of action for radiation injury. *See* Roberts v. Florida Power & Light Co. 146 F.3d 1305, 1306 (11th Cir. 1998), *cert denied* 525 U.S. 1139 (1999).

It is clear that in drafting the Act, Congress expressed a legislative intent to regulate radiological exposures with the underlying substantive foundations applied from state law. Plaintiffs allege that as a result of Defendant's negligence they were exposed to radiation and suffered injury and damages. (*See* Amended Complaint ¶9). Furthermore, Plaintiffs allege that the radiation doses caused them "physical injury and impact". (*See* Pltfs' Reply Brief in Support of Motion for Partial Summary Judgment p.2). Therefore, as a preliminary matter, this Court finds that the "physical impact or injuries" caused by the radiological exposure as alleged by Plaintiffs would qualify as a "nuclear incident" and bring the cause of action within the purview of the Act. Therefore, with respect to the nuclear exposure in this case, the Act preempts Plaintiffs' state law strict liability cause of action and Plaintiffs are limited to the PLA as their sole cause of action[1].

II. SUMMARY JUDGMENT ON PLAINTIFFS' CLAIMS FOR EMOTIONAL DISTRESS AND MEDICAL MONITORING UNDER THE PLA.

Summary judgment is appropriate when "there is no genuine issue as to any material fact, and the moving party is entitled to judgment as a matter of law." Fed. Rule Civ. P. 56(c). The moving party must initially identify those portions of the record before the Court which it believes establish an absence of material fact. <u>T.W. Elec. Serv., Inc. v. Pacific Elec. Contractors Ass'n.</u>, 809 F.2d 626, 630 (9th Cir. 1987). If the moving party adequately carries its burden, the party opposing summary judgment must then, "set forth specific facts showing that there is a

[1] The Court notes that Plaintiffs argue in their Response Brief in Opposition to Defendant's Motion to Dismiss Plaintiffs' Strict Liability Cause of Action and Substitute Sole Statutory Public Liability Cause of Action that if the Court finds that Plaintiffs have a "bodily injury" under the PLA, then they should be given leave to amend their amended complaint to assert federal question jurisdiction. However, Plaintiffs failed to file a Motion for Leave to Amend in accordance with Rule 15 F.R.Civ.P. and Local Rule 15.1 and the Court will not consider amending pleadings at this late date.

genuine issue for trial." Kaiser Cement Corp. v. Fischbach & Moore, Inc., 793 F.2d 1100, 1103-04 (9th Cir.), cert. denied, 479 U.S. 949 (1986).

All reasonable doubt as to the existence of genuine issues of material fact must be resolved against the moving party. Anderson v. Liberty Lobby, Inc., 477 U.S. 242 (1986). Nevertheless, "[d]isputes over irrelevant or unnecessary facts will not preclude a grant of summary judgment." T.W. Elect. Serv., 809 F.2d at 630 (citing, Liberty Lobby, 477 U.S. at 248). "A 'material' fact is one that is relevant to an element of a claim or defense and whose existence might affect the outcome of the suit. The materiality of a fact is thus determined by the substantive law governing the claim or defense." Id.

If a rational trier of fact might resolve disputes raised during summary judgment proceedings in favor of the nonmoving party, summary judgment must be denied. Matsushita Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 587 (1986). Thus, the Court's ultimate inquiry is to determine whether the "specific facts" set forth by the nonmoving party, viewed along with the undisputed background or contextual facts, are such that a rational or reasonable jury might return a verdict in its favor based on that evidence. Id. at 631.

A. Discussion

The Court must now determine if summary judgment is appropriate under the PLA with respect to Plaintiffs' claims for emotional distress and medical monitoring. Defendant argues that summary judgment is appropriate because when congress created the PLA a jurisdictional requirement was that a plaintiff's claim include a "bodily injury, sickness disease or death .... "42 U.S.C. § 2014 (w). Further, Defendant reasons that Congress did not include in the Act independent claims for emotional distress or medical monitoring from which Plaintiffs seek recovery and thus those claims should be dismissed.

Plaintiffs contend that they are entitled to seek damages for emotional distress because they suffered sub-cellular changes constituting bodily injury which resulted in the substantial reasonable fear of cancer. Plaintiffs further reason that by virtue of the exposure to radioactive material, Plaintiffs suffered, "physical injuries or impacts" at the sub-cellular level and that long term medical monitoring is appropriate.

In turn, Defendant argues that Plaintiff has no present medically diagnosable injury and the Ninth Circuit rejected the very sub-cellular argument that Plaintiffs present to this Court. *See* In re Berg Litigation, 293 F.3d 1127 (9th Cir. 2002) (holding that a bodily injury is a jurisdictional prerequisite to an emotional distress claim under the Act). In Berg, the Ninth Circuit applied section 2014(hh) to hold that Washington law permitting a claim for emotional distress without bodily injury is inconsistent with the Act and is preempted by it because bodily injury is a jurisdictional prerequisite to a PLA under the Act. Id. at 1131. Similar to the present facts, the plaintiffs in Berg were exposed to radiation and had not suffered any known present physical injury and nevertheless pursued claims for emotional distress and medical monitoring. Id. at 1130.

Plaintiffs note that Berg does not explicitly address whether sub-cellular changes constitute a "bodily injury". Plaintiffs further argue that the Court favorably cited Day v. NLO, 851 F.Supp. 869, 877 n. 3 (S.D.Ohio 1994) which held that if the plaintiffs could prove that they were exposed sufficiently to a high dose of radiation, this in itself will constitute a physical injury, sufficient to bring their action for emotional distress based on their exposure. Id. at 878.

It is clear under the Act, that the Court is without jurisdiction in this matter if Plaintiffs' claims for emotional distress did not arise out of a bodily injury, sickness, disease or death as a

result of an exposure to radiation. The Act also provides that "the substantive rules for decision in such action shall be derived from the law of the State in which the nuclear incident involved occurs, unless such law is inconsistent with the provisions of such section." 42 U.S.C. § 2014(hh).

Under Montana law, in order to recover for negligent infliction of emotional distress, the distress need only be serious or severe and does not necessarily need to be accompanied by a present bodily injury. *See* Contreraz v. Michelotti-Sawyers, 271 Mont. 300, 302 (1995). Therefore, like Berg, allowance of such a claim minus any "bodily injury" would be inconsistent with the provisions of the Act which require a "bodily injury". Consequently, the sole consideration left for the Court is whether the alleged sub-cellular changes caused by the radiation exposures present a "bodily injury" as contemplated by the Act.

In Berg, the Court notes that, " [t]he legislative history indicates that Congress added the words 'sickness' and 'disease' after 'bodily injury' in order to clarify what it meant by 'bodily injury'". Id. At 1131. In reviewing the legislative intent behind the Act, the Berg Court looks to the Nuclear Energy Liability Insurance Association (NELIA). Id. NELIA policies insured against bodily injury or property damage caused by nuclear incidents. Id. The Berg Court concluded that since NELIA policies did not provide coverage for purely emotional injuries, that Congress intended the same scope for the Act. Id.

Next, the Berg Court examines the Warsaw Convention which was motivated by the same concerns as the Act and notes that, "[b]oth the Supreme Court and our own cases addressing the meaning of Article 17 of the Convention have interpreted 'bodily injury' to include only a present physical injury. Id. At 1132, *citing* Eastern Airlines, Inc. v. Floyd, 499

U.S. 530, 542, 111 S.Ct. 1489, 113 L.Ed.2d 569 (1991) (Emphasis Supplied).

The Berg Court acknowledged that there is no threshold harmful dosage level for radiation because it can cause harm at any level. Id. At 1129 *citing* In re Three Mile Island Litig., 193 F.3d 613, 726-27 (3d Cir.1999). The Berg Court ultimately found that although the plaintiffs may have been exposed to radiation, that in and of itself did not qualify as a "bodily injury" sufficient to survive summary judgment with respect to the emotional distress claim. Therefore, while the Berg Court did not expressly address Plaintiffs' sub-cellular argument, this Court finds that the Berg Court implicitly rejected Plaintiffs' argument that sub-cellular changes due to radiation exposure minus any present physical injury constitutes a "bodily injury"as required by the Act in order for an emotional distress claim to survive summary judgment. Consequently, in accordance with Berg, the sub-cellular damage alleged by Plaintiffs, even though it may be directly linked with the increased likelihood of cancer, is not itself a present "bodily injury" and any PLA claim is premature.

Plaintiffs also assert a claim for medical monitoring. The Berg Court pointed out that similar to emotional distress claims, claims for medical monitoring are not included in the Act's jurisdictional provisions without "bodily injury, sickness, disease, or death ... or property damage," Id at 1133. Therefore, in light of this Courts findings that Plaintiffs' alleged sub-cellular changes do not amount to a present bodily injury, Plaintiffs' claim for medical monitoring also fails to meet the jurisdictional requirements of the Act.

Consequently, this Court is without jurisdiction over Plaintiffs' claims under the PLA until such time as Plaintiffs develop an objective demonstrable present bodily injury and summary judgment is appropriate.

Therefore, based on the foregoing,

IT IS HEREBY ORDERED:

1) that Defendants Motion to Dismiss Plaintiffs' Strict Liability Cause of Action and Substitute Sole Statutory Public Liability Cause of Action [Doc. #48] is **GRANTED;**

2) that Defendant's Motion for Summary Judgment on Plaintiffs' Public Liability Cause of Action *[Doc. # 50]* is **GRANTED;**

3) all other outstanding Motions are **DENIED as MOOT.**

The Clerk of Court is directed to enter judgment for Defendant in accordance with this order.

DONE and **DATED** this 22nd day of September, 2005.

RICHARD F. CEBULL
U. S. DISTRICT JUDGE

CERTIFICATE OF MAILING
DATE: 9/22/05
BY: tcl
I hereby certify that a copy of this Order was mailed to:
Alexander Blewett, III
Robert Sheridan
Donald Jose

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
COOPERATIVE AGREEMENT
LYNDON B. JOHNSON SPACE CENTER
2101 NASA Road 1, Houston, TX 77058

1. TO: National Space Biomedical Research Institute
c/o Baylor College of Medicine
Office of the President Attn: Ralph D. Feigin, M.D.
One Baylor Plaza
Houston, TX 77030

2. C. A. Number: NCC 9-58
3. Supplement: 1
4. Effective Date: April 1, 1997
5. Expiration Date: Sept. 30, 2002

6. For research entitled: National Space Biomedical Research Institute

7. Under the direction of (Institute Director): Laurence R. Young, Sc.D.

8. Award History
Previous Amount: $1,568,447
This action: $50,300,000
Total to date: $51,868,447

Funding History
Previous obligation: $1,568,447
This action: $0
Total obligation to date: $1,568,447

9. NASA Purchase Request Number: N/A
Accounting Code: N/A

PPC Code: RR
Appropriation Data: N/A

10. Points of Contact (name of office or individual, address, and telephone number):

Technical Officer:
Charles F. Sawin, Ph.D
NASA Johnson Space Center
Mail Code: SA; Houston, TX 77058
(281) 483-7202

Administration:
Steve Janney
NASA Johnson Space Center
Mail Code: BH23; Houston, TX 77058
(281) 483-3500 FAX: (281) 483-6041

Payment:
Funding and Payables Branch
NASA Johnson Space Center
Mail Code: LF2; Houston, TX 77058

Applicable enclosure(s), if checked:
__X__Provisions
__X__Special conditions
______Budget summaries and details

11. This Cooperative Agreement is awarded under the authority of 42 U.S.C. 2473 (c) (5), and is subject to all applicable laws and regulations of the United States in effect on the date this agreement is awarded, including but not limited to 14 CFR Part 1260 (Grants and Cooperative Agreements).

12. Purpose:
The purpose of this supplement is to establish the National Space Biomedical Research Institute.

UNITED STATES OF AMERICA

Nancy L Kennamer 5/30/97
Nancy L. Kennamer Date
Grants Officer

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE by: BAYLOR COLLEGE OF MEDICINE, Sole Member

Ralph D. Feigin 5/29/97
Ralph D. Feigin, M.D. Date
President, Baylor College of Medicine

EXHIBIT
D

13. COOPERATIVE AGREEMENT SPECIAL CONDITION (July 1996)

(a) This award is a Cooperative Agreement as it is anticipated that there will be substantial NASA involvement during performance of the effort. NASA and the Recipient mutually agree to the following statement of anticipated cooperative interactions which may occur during the performance of this effort:

The scope of the National Space Biomedical Research Institute (NSBRI) includes the definition, development, and implementation of a Space Biomedical Research Program which emphasizes human life science ground-based and flight research. The NSBRI Management Plan serves as the detailed definition of the scope of work under this Cooperative Agreement, and is hereby incorporated by reference. The activities to be supported through the Cooperative Agreement are 1) core - Institute administration/operations and research; 2) grants - implementation of Institute proposals that were successful in the NASA yearly solicitation process and potential management of non-Institute grants, and 3) projects and selected science management functions.

The NASA Johnson Space Center (JSC) will make available to the Institute its considerable knowledge and expertise in the area of human space life sciences and the associated facilities and assets it has developed in more than thirty years of human space flight.

(b) The terms "Grant" and "Recipient" mean this Cooperative Agreement and NSBRI respectively, wherever the terms appear in provisions and special conditions included in this agreement.

(c) NASA's ability to participate and perform its collaborative effort under this Cooperative Agreement is subject to the availability of appropriated funds and nothing in this Cooperative Agreement commits the United States Congress to appropriate funds therefor.

14. INCREMENTAL FUNDING (July 1996)

Only $1,568,447 of the amount indicated on the face of this award is available for payment and allotted to this award. NASA contemplates making additional allotments of approximately $2,500,000 quarterly. These funds will be obligated as appropriated funds become available without any action required by the Recipient. The Recipient will be given written notification by the NASA Grants Officer. NASA is not obligated to reimburse the Recipient for the expenditure of amounts in excess of the total funds allotted by NASA.

15. MULTIPLE YEAR COOPERATIVE AGREEMENT (July 1996)

This is a multiple year Cooperative Agreement. Contingent on the availability of funds, scientific progress of the project and continued relevance to NASA programs, NASA anticipates continuing core support at approximately the following levels (the core support is stated in 1997 dollars and will be adjusted annually by the percentage increase in the Consumer Price Index):

6/1/1997-9/30/1997, $1.3 million
10/1/1997-9/30/2001, $10 million per year
10/1/2001-9/30/2002, $9 million

16. EXTENSIONS

The Government anticipates that this Cooperative Agreement will have a 5 1/2-year basic period with three 5-year optional extensions. The Government is not obligated to execute an extension to the Cooperative Agreement if it determines that doing so is not in its best interest; in other words, the Recipient will not have the right to have the Cooperative Agreement continued.

Six months prior to the expiration date, the Government will notify the Recipient in writing of its intent to extend the Cooperative Agreement for five years. The Government may request an updated proposal to be submitted within 60 days after receipt of the notification. If a proposal is requested, details will be provided at the time of the request. A supplement will be executed by the Grants Officer to extend the Cooperative Agreement.

In the event this Cooperative Agreement will not be renewed, there will be a 6-month phase out period (following the expiration date) with a linear reduction in funds to assure an orderly completion of ongoing activities.

17. PUBLICATIONS AND REPORTS
The Recipient will be required to provide the following formal written reports:

a. Monthly Activity Report
A brief monthly activity report shall be submitted highlighting science and technology activities accomplished during the month and activities proposed for the upcoming month. One copy of the monthly activity report shall be submitted by the 15th day of the month following the month being reported to each person on the distribution list at the following addresses:

NASA Lyndon B. Johnson Space Center
Attn:
2101 NASA Rd 1
Houston, TX 77058

Distribution:
BH23/S. Janney
SA/C. Sawin

b. Cost Reporting
Quarterly cost reports, supplementing the SF272, shall be submitted on the format and in accordance with the instructions in Attachment 1 with a copy of the SF272. The report shall be submitted 15 working days following the end of each Federal fiscal quarter. One copy of the report shall be distributed to each of the following individuals at the addresses stated above.

Distribution:
BH23/S. Janney
SL/BH/P. Halyard
SA/C. Sawin

c. Annual Scientific and Technical Report
An annual scientific and technical report shall be submitted summarizing the year's accomplishments and the overall plan for the next year's activities. The annual scientific and technical report shall discuss the scientific research being pursued, actual or anticipated results, and the specific technologies being pursued. Any pertinent information resulting from the Recipient's Board of Directors activities should be included in this report. The report is due each year by September 30. One copy of the report shall be submitted to each person on the following distribution list at the addresses noted above:

Distribution:
BH23/S. Janney
SA/C. Sawin

One micro-reproducible copy to:
Center for AeroSpace Information (CASI)
Attn: Accessioning Department
800 Elkridge Landing Road
Linthicum Heights, MD 21090-2934

NASA encourages the widest practicable dissemination of research results at any time during the course of the Cooperative Agreement. All information disseminated as a result of the Cooperative Agreement, shall contain a statement which acknowledges NASA's support and identifies the Cooperative Agreement by number. Prior approval by the NASA Grants Officer is required only where the Recipient requests that the results of the research be published in a NASA scientific or technical publication. Two copies of each draft publication shall accompany the approval request.

18. REVIEWS

a. Comprehensive Review

NASA will conduct a comprehensive review of the Recipient's activities and progress following the third year of each 5 year increment. This review will be headed by NASA's chief scientist and will include senior NASA management as well as participation by members of NASA's science advisory panels.

b. Periodic Reviews

NASA will conduct periodic reviews of the Recipient's activities as agreed upon.

19. KEY PERSONNEL AND FACILITIES

The personnel listed below are considered essential to the work being performed under this Cooperative Agreement. Before removing, replacing, or diverting any of the listed or specified personnel, the Recipient shall (1) notify the Grants Officer reasonably in advance and (2) submit justification (including proposed substitutions) in sufficient detail to permit evaluation of the impact on this Cooperative Agreement. The Recipient shall make no diversion without the Grants Officer's written consent; provided that the Grants Officer may ratify in writing the proposed change, and that ratification shall constitute the Grants Officer's consent required by this clause. The list of personnel shown below may, with the consent of the contracting parties, be amended from time to time during the course of the Cooperative Agreement to add or delete personnel.

Name	Title
Laurence R. Young, Sc.D.	Director
Ronald J. White, Ph.D.	Associate Director
Bobby R. Alford, M.D.	Chairman, Board of Directors

20. INSURANCE

The Recipient shall obtain and maintain insurance coverage as follows for the performance of the Cooperative Agreement:

(a) Worker's compensation and Recipient's liability insurance as required by applicable Federal and state worker's compensation and occupational disease statutes. If occupational diseases are not compensable under those statutes, the Recipient shall cover them under the liability section of the insurance policy, except when it would not be practical. The Recipient's liability coverage shall be at least $100,000, except in States with exclusive or monopolistic funds that do not permit private carriers to write worker's compensation.

(b) Comprehensive general (bodily injury) liability insurance of at least $10,000,000 with a deductible of no more than $250,000 per occurrence.

(c) Motor vehicle liability insurance written on the comprehensive form of policy which provides for bodily injury and property damage liability covering the operation of all motor vehicles used in connection with performing the Cooperative Agreement. Policies covering motor vehicles operated in the United States shall provide coverage of at least $200,000 per person and $500,000 per occurrence for bodily injury liability and $20,000 per occurrence for property damage. The amount of liability coverage on other policies shall be commensurate with any legal requirements of the locality and sufficient to meet normal and customary claims.

(d) Comprehensive general and motor vehicle liability policies shall contain a provision worded as follows: "The insurance company waives any right of subrogation against the United States of America which may arise by reason of any payment under the policy."

21. <u>IDENTIFICATION OF EMPLOYEES</u>
At all times while on Government property, the Recipient, subcontractors, their employees and agents shall wear badges which will be issued by the NASA Contract Badge and Pass Office, located in building No. 110. Badges will be issued only between the hours of 7:00 a.m. and 4:00 p.m., Monday through Friday. Each individual who wears a badge will be required to sign personally for the badge. The Recipient will be held accountable for these badges, and immediately after completion of work they shall be returned to NASA Contract Badge and Pass Office. Failure to turn in badges upon completion of the work may result in final payment being delayed.

22. <u>HUMAN RESEARCH POLICY AND PROCEDURES</u>
The Recipient shall follow the human research policy and procedures, stated in NMI 7100.8B, Protection of Human Research Subjects," and JMI 7170.2A "Scientific Misconduct with Regard to Human Research" and shall furnish to the Grants Officer, upon request, copies of protocols and Recipient documents showing Contractor Human Research Committee approval of such protocols.

23. <u>SAFETY AND HEALTH</u>
(a) The Recipient shall take all reasonable safety and health measures in performing under this Cooperative Agreement. The Recipient shall comply with all Federal, State, and local laws applicable to safety and health in effect during the term of this Cooperative Agreement and with the safety and health standards, specifications, reporting requirements, and provisions set forth in the Cooperative Agreement. The Recipient's safety and health plan, which describes the Recipient's implementation of its safety and health responsibilities, is incorporated by reference.
(b) The Recipient shall take or cause to be taken any other safety and health measures the Grants Officer may reasonably direct.
(c) The Recipient shall immediately notify and promptly report to the Grants Officer or a designee any accident, incident, or exposure resulting in fatality, lost-time occupational injury, occupational disease, contamination of property, or property loss of $25,000 or more arising out of work performed under this Cooperative Agreement. The Recipient is not required to include in any report an expression of opinion as to the fault or negligence of any person. The Recipient shall investigate all work-related incidents or accidents to the extent necessary to determine their causes and furnish the Grants Officer a report in such form as the Grants Officer may require, of the investigative findings and proposed or completed corrective actions.
(d) (1) The Grants Officer may notify the Recipient in writing of any noncompliance with this clause and specify corrective actions to be taken. The Recipient shall promptly take and report any necessary corrective action.
(2) If the Recipient fails or refuses to institute prompt corrective action in accordance with subparagraph (d)(1) of this clause, the Grants Officer may temporarily suspend work under this Cooperative Agreement or any other remedy available to the Government in the event of such failure or refusal.

(e) The Recipient (or subcontractor) shall insert the substance of this clause, including this paragraph (e) with appropriate changes or designations of the parties, in subcontracts of every tier that (1) amount to $1,000,000 or more (unless the Grants Officer makes a written determination that it is not required), or (2) regardless of dollar amount, involve the use of hazardous materials or operations.

(f) Authorized Government representatives of the Grants Officer shall have access to and the right to examine the sites or areas where work under this contract is being performed in order to determine the adequacy of the Recipient's safety and health measures under this clause, on request.

(g) As a part of the Recipient's safety plan (and health plan, when applicable) the Recipient shall furnish a list of all hazardous operations to be performed on Government property or offsite involving Government personnel or property. For those operations which the Recipient is uncertain about its inclusion in this clause, the Recipient shall notify the Government whenever any of the following criteria apply: (1) it involves Government property in excess of $25,000 in replacement value; (2) it poses a safety or health risk to Government employee(s); or (3) it will be performed on Government property. Before hazardous operations commence, the Recipient shall submit for NASA concurrence either or both of the following as required by the Grants Officer:

(1) Written hazardous operating procedures for all hazardous operations.

(2) A certification program, where applicable, for personnel involved in hazardous operations.

(h) The Recipient shall identify in its plan any safety and health requirements that must be followed by the Government representatives or its agents at the Recipient's facilities. The Recipient will be responsible for providing basic information and the requisite orientation-type training of Government representatives or its agents. The Government reserves the right to waive any training requirements when responding to urgent situations such as a mishap.

24. RESPONSIBILITIES OF THE NASA TECHNICAL OFFICER

The Technical Officer shall have the authority to represent NASA in any discussions regarding the activities being conducted under this Cooperative Agreement. The Technical Officer shall have the authority to approve or disapprove reports and any technical information the Recipient is required to submit to NASA for approval. The Technical Officer is not authorized to issue and the Recipient shall not follow any technical advice which constitutes work which is not contemplated under this agreement; which in any manner causes an increase or decrease in the resource sharing or in the time required for performance; which has the effect of changing any of the terms or conditions of the Cooperative Agreement; or which interferes with the Recipient's right to perform the project in accordance with the terms and conditions of this Cooperative Agreement, unless jointly agreed upon and the Cooperative Agreement is modified accordingly.

25. PROVISIONS INCORPORATED BY REFERENCE

The following provisions are incorporated by reference. Provisions incorporated by reference have the same force and effect as if they were given in full text. Source: 14 CFR Part 1260. Copies of the Code of Federal Regulation volumes are available in many libraries and for purchase from the Superintendent of Documents, Government Printing Office, Washington, DC 20420. Copies of OMB Circulars referenced in the provisions may be obtained from the Office of Administration, Publications Unit, New Executive Office Building, Washington, DC 20503. An index of existing Circulars is contained in 5 CFR 1310.

Full Text Reference	Title(Date)
1260.23	Termination and Enforcement (July 1996)
1260.24	Change in Principal Investigator or Scope (July 1996)
1260.25	Allowable Costs (July 1996)
1260.26	Financial Management (July 1996)
1260.27	Equipment and Other Property (July 1996)
1260.28	Patent Rights (July 1996)

1260.29	Rights in Data (July 1996)
1260.30	National Security (July 1996)
1260.31	Nondiscrimination (July 1996)
1260.32	Subcontracts (July 1996)
1260.33	Clean Air and Water (July 1996)
1260.34	Procurement Standards (July 1996)
1260.35	Foreign National Employee Investigative Requirements (July 1996)
1260.36	Travel and Transportation (July 1996)

26. ATTACHMENT

Attachment 1 - Cost Reporting Format

Attachment I

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE (NSBRI) QUARTERLY COST REPORT

I. COST DEFINITION

Cost is the financial measurement of resources used in accomplishing a specified purpose, such as performing a service, carrying out an activity, acquiring an asset, or completing a unit of work or a project. Costs reported to NASA by the Recipient are used as the basis for recording a liability of the U.S. Government. The quarterly cost report will be used for planning, monitoring, and controlling resources. The U. S. Government uses the accrual method of accounting. The accrual method of accounting requires that the cost be reported to NASA in the period in which the benefit is received without regard to the time of payment. Examples of accrual accounting for common cost elements to be reported are as follows:

COST ELEMENT	DESCRIPTION
Labor	Reported to NASA as hours/costs (including benefits) are incurred.
Subcontracts	Subcontractors are required to report cost to NASA using the accrual method of accounting, the same format, and the same time period as the Recipient's quarterly cost report. For firm-fixed price subcontracts with a contract value greater than $500,000, the Recipient is required to document the reporting methodology used to generate the accrual and provide the information to the Grants Officer.
Facility Costs/Leases	Reported to NASA using a proration over the life of the lease.
Consultants	Reported to NASA as hours/costs are incurred.
Equipment, Materials, or Supplies (commercial off-the-shelf)	Generally reported to NASA when received and accepted by the Recipient.
Travel	Travel is reported as incurred, generally using the dates of travel as guidance for reporting cost.
Indirect Costs	The indirect cost rate is negotiated between the Recipient (non-profit/educational institution) and the single responsible cognizant agency.

Cost Sharing	Any funds received by the Recipient from sources other than NASA will be reported in the period in which they are received. The costs covered by these funds will be added to the total estimated costs expended to calculate the total cost of the program. A supplement must be attached to the quarterly report identifying each contributing organization with an explanation of the amount of funds received from that organization and why they were received.
Total Program Costs	These costs are the sum of the total costs and the amount of cost sharing.

Prior period cost adjustments will be reported in the prior quarter actual cost column. The reason for the adjustment and the amount of the adjustment will be footnoted directly on the quarterly cost report.

The quarterly cost report is due no later than the 15th working day of the month following the quarter being reported.

II. COMPLETION INSTRUCTIONS

The following instructions refer to the attached quarterly cost report format. These instructions relate to each individual column shown in the quarterly cost format.

1. CURRENT QUARTER

(a) This Quarter Actual - This column will show all costs expended during the current quarterly reporting period.

(b) This Quarter Planned - This column will show the Recipient's previous reporting period planned quarterly costs for the current quarterly report. Therefore, these costs will be the sum of the monthly costs from column 2(a) of the previous quarterly report.

(c) Cumulative Actual - This column will show all cumulative costs expended through end of the current quarterly reporting period.

(d) Cumulative Planned - This column will show cumulatively what the Recipient had projected from the previous quarter. Therefore, this column is the sum of the cumulative actual from the previous quarterly report and column 1(b) of the current quarterly report [column 1(b) of the current quarterly report is the same as the sum of the monthly costs from column 2(a) of the previous quarterly report as explained above.

2. ESTIMATED COST TO COMPLETE

(a) Next Quarter - This column will reflect the amount of expenditures that the Recipient plans to spend in the quarter following the current quarterly reporting period. The Recipient will insert the costs projected for the next quarter by month.

(b) Balance for Fiscal Year - This column will reflect the amount of expenditures that the Recipient plans to spend from the end of the next quarterly reporting period to the end of the current Government fiscal year. If the current quarterly reporting period happens to end when the current fiscal year ends, then this column will reflect zero expenditures.

(c) Balance of the Cooperative Agreement (C.A.) - This column will reflect the balance of the Cooperative Agreement value beginning with the next fiscal year. Therefore, this column will be a "plug in" number to make the sum of columns 1(c), all of 2(a), 2(b), and 2(c) equal the Cooperative Agreement value.

3. COOPERATIVE AGREEMENT VALUE

This column shows the current negotiated Cooperative Agreement value. The sum of columns 1(c), all of 2(a), 2(b), and 2(c) will equal the Cooperative Agreement value.

4. OUTSTANDING COMMITMENTS

This column will reflect all the outstanding commitments or unfilled orders as of the current report date. Outstanding commitments are supplies, materials, or anything that has been ordered and is waiting to be received.

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE (NSBRI)
QUARTERLY COST REPORT

Period from: __________ to: __________

COST DESCRIPTION	1. CURRENT QTR				2. ESTIMATED COST TO COMPLETE					3. COOP. AGR. VALUE	4. OUTSTND COMM.
	(a) This Quarter Actual	(b) This Quarter Planned	(c) Cum to date Actual	(d) Cum to date Planned	(a) Next Quarter Projection			(b) Balance of Fiscal Yr	(c) Balance of Coop Agr		
					Month of ____	Month of ____	Month of ____				
Labor hours											
Labor Dollars											
Other Direct Costs											
Subcontracts											
Facility Costs											
Consultants											
Equipment											
Supplies											
Travel											
Other											
Total Other Direct Costs											
Other Applicable Costs											
Subtotal											
Indirect Costs ____%											
TOTAL COSTS											
Cost Sharing											
TOTAL PROGRAM COSTS											

MARSHALL DENNEHEY WARNER
COLEMAN & GOGGIN
BY: DANIEL J. SHERRY, ESQUIRE
ATTORNEY I.D. NO. 21654
620 Freedom Business Center, Suite 300
King of Prussia, PA 19406
(610) 354-8260 (610) 354-8299 (Facsimile)
Attorney for Defendants: Hospital of the University of PA,
University of PA, Perelman School of Medicine University of PA,
Trustees of the University of PA, Ann R. Kennedy, D.S.C.,
Gary Kao, M.D. and Michelle Alonso-Basanta, M.D.

Estate of Jeffrey H. Ware, By Barbara Boyer, Individually,	:
On Behalf of Wrongful Death Beneficiaries and as	:
Administratrix of Estate of Jeffrey H. Ware	:
vs.	:
Hospital of the University of Pennsylvania, and	: Case No.
University of Pennsylvania, and Perelman School of Medicine	:
University of Pennsylvania, and Trustees of the University of	:
Pennsylvania, and Ann R. Kennedy, D.S.C. and	:
Gary Kao, M.D. and Michelle Alonso-Basanta, M.D., and	:
National Space Biomedical Research Institute and	:
Center for Acute Radiation Research	:

PRAECIPE TO FILE NOTICE OF REMOVAL

TO: Prothonotary
Court of Common Pleas
Philadelphia County
City Hall, PA 19107

Please take notice that the Defendants, Hospital of the University of Pennsylvania, and University of Pennsylvania, and Perelman School of Medicine University of Pennsylvania, and Trustees of the University of Pennsylvania, and Ann R. Kennedy, D.S.C., and Gary Kao, M.D., Michelle Alonso-Basanta, M.D., National Biomedical Research Institute and Center for Acute Radiation Research, in a lawsuit styled *Estate of Jeffrey H. Ware, By Barbara Boyer,*

EXHIBIT
E

Individually, on Behalf of Wrongful Death Beneficiaries and as Administratrix of Estate of Jeffrey H. Ware vs. Hospital of the University of Pennsylvania, University of Pennsylvania, Perelman School of Medicine University of Pennsylvania, Trustees of the University of Pennsylvania, Ann R. Kennedy, D.S.C. Gary Kao, M.D. Michelle Alonso-Basanta, M.D., and National Space Biomedical Research Institute and Center for Acute Radiation Research, October Term, 2013, No. 001927, in the Court of Common Pleas of Philadelphia County, Pennsylvania have filed a Notice of Removal of said action to the United States District Court for the Eastern District of Pennsylvania on the 2nd day of January, 2014. (A true and correct copy of said Notice, including Exhibits is attached hereto.)

Respectfully submitted:

MARSHALL DENNEHEY WARNER
COLEMAN & GOGGIN

BY: DANIEL J. SHERRY, ESQUIRE
ATTORNEY I.D. NO. 21654
620 Freedom Business Center, Suite 300
King of Prussia, PA 19406
(610) 354-8260 (610) 354-8299 (Facsimile)
djsherry@mdwcg.com
Attorney for Defendants: Hospital of the University of PA, University of PA, Perelman School of Medicine University of PA, Trustees of the University of PA, Ann R. Kennedy, D.S.C., Gary Kao, M.D. and Michelle Alonso-Basanta, M.D.

CERTIFICATE OF SERVICE

I do hereby certify that service of a true and correct copy of the within Notice of Removal on behalf of Defendants, Hospital of the University of Pennsylvania, and University of Pennsylvania, and Perelman School of Medicine University of Pennsylvania, and Trustees of the University of Pennsylvania, and Ann R. Kennedy, D.S.C., and Gary Kao, M.D., Michelle Alonso-Basanta, M.D., National Biomedical Research Institute and Center for Acute Radiation Research was served on this date upon the following persons by electronic filing:

Aaron J. Freiwald, Esquire
Layser & Freiwald, P.C.
1500 Walnut Street, 18th Floor
Philadelphia, PA 19102

Donald Jose, Esquire
Jose and Associates
108 Tramore Circle
Malvern, PA 19355

Dean F. Murtagh, Esquire
Kathryn A. Dux, Esquire
German Gallagher & Murtagh
The Bellevue, Fifth Floor
200 South Broad Street
Philadelphia, PA 19102

MARSHALL, DENNEHEY, WARNER, COLEMAN & GOGGIN

BY:______________________________
DANIEL J. SHERRY, ESQUIRE
Attorney for Defendants, Hospital of the University of PA, University of PA, Perelman School of Medicine University of PA, Trustees of the University of PA, Ann R. Kennedy, D.S.C., Gary Kao, M.D. and Michelle Alonso-Basanta, M.D.

Date: January 2, 2014

CERTIFICATE OF SERVICE

I do hereby certify that service of a true and correct copy of the within Notice of Removal on behalf of Defendants, Hospital of the University of Pennsylvania, and University of Pennsylvania, and Perelman School of Medicine University of Pennsylvania, and Trustees of the University of Pennsylvania, and Ann R. Kennedy, D.S.C., and Gary Kao, M.D., Michelle Alonso-Basanta, M.D., National Space Biomedical Research Institute and Center for Acute Radiation Research was served on this date upon the following persons by first class mail:

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BY:____________________________
DANIEL J. SHERRY, ESQUIRE
Attorney for Defendants, Hospital of the University of PA, University of PA, Perelman School of Medicine University of PA, Trustees of the University of PA, Ann R. Kennedy, D.S.C., Gary Kao, M.D. and Michelle Alonso-Basanta, M.D.

Date: January 2, 2014